

## REMARKS

### Information Disclosure Statement

The Applicants wish to thank the Examiner for pointing out our non-compliance under 37 C.F.R. §1.98(a)(2) due to the missing Borodic *et al.* publication. The Applicants have submitted a copy of this publication for the Examiner's inspection.

### Oath/Declaration

The Examiner objects to the submitted 37 C.F.R. §1.63 oath as allegedly being non-compliant pursuant to 37 C.F.R. §1.52(c) because non-initialed and/or non-dated alterations were made to the oath. The Applicants respectfully disagree with this objection.

Rule §1.52(c)(1) states:

Any interlineation, erasure, cancellation or other alteration of the application papers filed must be made **before the signing** of any accompanying oath or declaration pursuant to §1.63 referring to those application papers and should be dated and initialed **or signed by the applicant on the same sheet of paper**. Application papers containing alterations made after the signing of an oath or declaration referring to those application papers must be supported by a supplemental oath or declaration under §1.67. In either situation, a substitute specification (§1.125) is required if the application papers do not comply with paragraphs (a) and (b) of this section. (Emphasis added)

The Applicants respectfully submit that 1) the corrections were executed by the inventor before the actual signing of the oath; and 2) the appropriate signature is present on the same sheet of paper. Thus, the Applicants respectfully contend that the submitted 37 C.F.R. §1.63 oath is fully compliant and that request of a new supplemental 37 C.F.R. §1.67 oath is inappropriate. Therefore, the Applicants respectfully request withdrawal of the non-compliance objection under 37 C.F.R. §1.52(c).

### Amendments to the Specification

First, the Applicants thank the Examiner for pointing out the informalities contained within the specification and have corrected all typographical errors. Specifically, the specification was amended to:

1. Replaced "TeNT" with "TeTx" on page 2, line 5; page 2, line 10; page 2, line 23; page 3, line 7; page 3, line 12; page 4, line 5; page 4, line 7; page 4, line 10; page 17, line 11; page 20, line 22; page 20, line 24; and page 21, line 13.
2. Replace "TeT%X" with :TeTx" on page 14, line 4.
3. Replaced "calmodilin" with "calmodulin" on page 24, line 1.

Second, the Applicants have updated the Sequence Listing to include sequences identified by the Examiner and have amended the specification by including SEQ ID NOs for all recited sequences. Specifically:

1. The specification was amended to recite amino acid sequences EXXYXQS and EXXYXQG disclosed on page 18, line 19 and identification of said sequences as SEQ ID NO: 22 and SEQ ID NO: 23, respectively..
2. Amino acid sequence HELIH disclosed on page 20, line 24, HELNH disclosed on page 20, line 25 and HEALTH disclosed on page 20, line 25 were added to the Sequence Listing as SEQ ID NO: 25, SEQ ID NO: 26 and SEQ ID NO: 27, respectively and the specification was amended to include these SEQ ID NOs.
3. Amino acid sequence Ile-Glu-Gly-Arg disclosed on page 27, line 24 was added to the Sequence Listing as SEQ ID NO: 28 and the specification was amended to include this SEQ ID NO.
4. Amino acid sequence GEKLYDDDDKDRWGSSR disclosed on page 37, line 18 was added to the Sequence Listing as SEQ ID NO: 29 and the specification was amended to include this SEQ ID NO.

Third, the Applicants have amended the specification to correct the informalities associated with the use of trademarks and to include generic terminology for the use of TWEEN 20<sup>®</sup> disclosed on page 34, line 5 and TALON<sup>®</sup> disclosed on page 50, line 17.

Fourth, as per the Examiner's suggestion, the Applicants have corrected several minor spelling or grammatical errors. Specifically, the specification was amended to:

1. Replace "neurotoxoin" with "neurotoxin" on page 5, line 11.
2. Replace "an" with "in" on page 17, line 22.
3. Replaced "primer" with "primers" on page 28, line 26.
4. Replaced "frangment" with "fragment" on page 47, line 4. 21-27 through page 28, lines 1-5] with the following paragraph:
5. Replaced "contain" with "contains" on page 50, line 1.

The Applicants hereby state that all amendments do not add new subject matter to the specification.

The Examiner objects to the abstract [page 65, lines 3-6] on the grounds that the first sentence allegedly contains no verb. The first sentence of the abstract is as follows "Compositions **comprising** activatable recombinant neurotoxins and polypeptides derived therefrom." The Applicants respectfully submit that the first sentence of the abstract does contain a verb, namely "comprising." Therefore, the Applicants respectfully request the withdrawal of the objection.

## Amendments to the Claims

The Applicants respectfully ask the Examiner to replace all prior versions and listings of claims in the instant application with the listing of claims currently provided. Claims 35, 36 and 37 are new, Claims 20, 26, 32 and 33 were amended.

The Examiner objects to Claim 32 as being improper under 37 C.F.R. §1.75(c) on the grounds that a multiple dependent claim cannot depend from any other multiple dependent claim. The Applicants have amended Claim 32 and added new claims (Claim 35, 36 and 37) to correct this improper claim form. The Applicants wish to stress that Claim 32 was amended for formality purposes only and are not explicitly or implicitly surrendering equivalents or narrowing the scope of any of the claimed subject matter. The Applicants respectfully submit that the language of Claim 32 is now in proper format and request withdrawal of the 37 C.F.R. §1.75(c) objection.

The Examiner objects to Claim 26 as being improper under 37 C.F.R. §1.75(c) on the grounds of informal claim language. The Applicants have amended Claim 26 as per the Examiner's suggestion. The Applicants wish to stress that Claim 26 was amended for formality purposes only and are not explicitly or implicitly surrendering equivalents or narrowing the scope of any of the claimed subject matter. The Applicants respectfully submit that the language for Claim 26 is now in proper format and request withdrawal of the 37 C.F.R. §1.75(c) objection.

## Rejection Pursuant to 35 U.S.C. §112, ¶2 Indefiniteness

The Examiner has rejected Claim 33 as allegedly lacking definiteness under 35 U.S.C. §112, ¶2 since Claim 33 depends from a canceled claim. The Applicants have amended Claim 33 to depend from either of Claim 21 or 22. The Applicants respectfully submit that the alleged indefiniteness of Claim 33 stemmed from a restriction requirement imposed by the Examiner. Therefore, the Applicants wish to stress that Claim 33 was amended for formality purposes only and are not explicitly or implicitly surrendering equivalents or narrowing the scope of any of the claimed subject matter. The Applicants respectfully submit that the language for Claim 33 is now in proper format and request withdrawal of the 35 U.S.C. §112, ¶2 indefinite rejection.

The Examiner has also rejected Claim 33 as allegedly lacking definiteness under 35 U.S.C. §112, ¶2 for failing to recite an essential step. The Applicants respectfully traverse this rejection and ask for reconsideration under 37 C.F.R. §1.111.

As cited in the *Manual of Patent Examining Procedure*, 8<sup>th</sup> edition, February 2003 revision (hereafter "*MPEP*"), the courts have interpreted the standard for determining indefiniteness due to unclaimed essential matter under 35 U.S.C. §112, ¶2 as follows:

... a claim which fails to interrelate essential elements of the invention **as defined by applicant(s) in the specification** may be rejected under 35 U.S.C. 112, second paragraph, for failure to point out and distinctly claim the invention. See *In re Venezia*, 530 F.2d 956, 189 USPQ 149 (CCPA 1976); *In re Collier*, 397 F.2d 1003, 158 USPQ 266 (CCPA 1968). (Emphasis added)  
*MPEP*, §2172.01.

The Applicants respectfully disagree that any unclaimed essential matter was omitted from Claim 33. The Applicants respectfully submit that the additional step suggested by the Examiner is not an essential step as defined by the instant specification, but rather a routine step that would be well-known and commonly used to one skilled in the pertinent art. However, in order to provide more clarity, Claim 33 was amended to add a third step directed toward purification. The Applicants wish to stress that Claim 33 was amended for clarity purposes only and are not explicitly or implicitly surrendering equivalents or narrowing the scope of any of the claimed subject matter. Therefore, the Applicants respectfully submit that Claim 33 has not omitted an essential step and request withdrawal of the 35 U.S.C. §112, ¶2 indefinite rejection.

### Rejection Pursuant to 35 U.S.C. §102(b) and (e) Anticipation

The Examiner has rejected Claims 20-33 as allegedly anticipated under 35 U.S.C. §102(b) by PCT patent publication WO98/07864 (hereafter "the '864 application"). The Applicants respectfully traverse this rejection and ask for reconsideration under 37 C.F.R. §1.111.

As discussed in MPEP §2131, "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Thus, a single prior art reference must **enable** and literally or inherently **teach each and every limitation** of the challenged claim. In order for a limitation to be inherent it must inevitably follow from the teaching of the prior art.

The Applicants note that Claim 20 was amended to indicate that the third amino acid sequence is not cleaved by a **human protease**. Basis for this amendment can be found on page 9, line 19 to page 10, line 5, of the instant application. The Applicants respectfully submit that alleged anticipation rejection is now moot for the following three reasons.

First, the Examiner contends that Claim 20 is anticipated by the disclosure of the plasmid construct encoding a single chain polypeptide termed LH423/A in the '864 publication. This plasmid construct does not anticipate amended Claim 20 or any other pending claim of the instant application. Specifically, the plasmid construct does not contain the "first portion encoding a first amino acid sequence region comprising a binding element", as required in Claim 20. Moreover, the LH423/A construct does not encode a fourth amino acid sequence comprising a protease cleavage site. See also Figure 2 from the '864 publication.

Second, the Examiner states that the '864 publication discloses "a plasmid variant incorporating a protease cleavage site for Factor Xa on page 20, lines 2-10." However, this disclosure does not anticipate the amended Claim 20 (or claims dependent thereupon), since the resulting construct still does not contain a binding element, such as one present in the H<sub>C</sub> portion of BoNT/A, and the protease cleavage site is cleaved by a human protease (Factor Xa).

Third, the disclosure of the specific examples containing various carboxy terminal domains described on page 20 and top of page 21 of the '864 publication does not anticipate amended Claim 20, for the same reason as given in the last paragraph; the protease cleavage site located in the fourth amino acid sequence region is still Factor Xa, a human protease.

The Examiner also rejects Claim 20-33 as allegedly anticipated by U. S. patent publication US 6,461,617 (hereafter the "617 patent). The Applicants respectfully traverse this rejection and ask for reconsideration under 37 C.F.R. §1.111. The Applicants respectfully submit that the '617 publication contains essentially identical subject matter to the '864 publication and the reasons for rejection are likewise identical. Thus, the Applicants grounds for traversal are also the same as indicated above.

Therefore, the Applicants respectfully submit that the subject matter of the instant application is novel and not anticipated by '864 and '617 publications and respectfully request withdrawal of the 35 U.S.C. §102(b) and (e) anticipation rejections for Claims 20-33.

#### **Rejection Pursuant to 35 U.S.C. §103(a) Obviousness**

The Examiner has rejected Claims 20-29 and 31-33 as allegedly obvious under 35 U.S.C. §103 over the '617 publication discussed above. Specifically the Examiner argues that the '617 patent mentions an invention can be practiced with both botulinum and tetanus toxins. The Applicants respectfully traverse this rejection and ask for reconsideration under 37 C.F.R. §1.111.

According to *MPEP* §2143, to render a pending claim obvious, a reference must expressly or impliedly teach or suggest the claimed subject matter.

The Applicants respectfully submit that the claimed subject matter indicates that the protease cleavage site cannot be susceptible to the activity of a human protease, a point made more clear in Claim 20 as now amended. The Applicants respectfully draw the Examiner's attention to the importance of expressing a non-toxic (or less toxic) neurotoxin, namely, preventing accidental exposure of humans to activated neurotoxin inadvertently cleaved by a human protease. The '617 publication actually teaches inclusion of a human protease cleavage site. Thus, the claim subject matter of the instant specification clearly represents a real advantage and significant improvement that is completely unsuggested by the '617 publication.

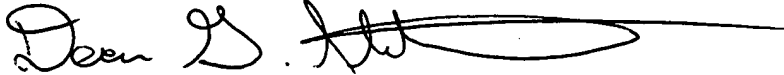
Therefore, the Applicants respectfully submit that nothing in the '617 publication discloses or suggests such compositions and respectfully request withdrawal of the 35 U.S.C. §103(a) obviousness rejection for Claims 20-29 and 31-33.

Serial No.: 09/648,692 Activatable Recombinant Neurotoxin  
Filed: August 25, 2000

### CONCLUSION

For the above reasons the claims are now thought to be in condition for allowance, and the Applicants respectfully urge the Examiner to issue a Notice to that effect. Please use Deposit Account 01-0885 for the payment of the extension fees or any other fees due in connection with the current response.

Respectfully submitted,



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